REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the claims

No claims are newly amended, added or cancelled. Claims 1-13, 15, 24 and 27-39 were previously cancelled and claims 14, 16-23, 25 and 26 are pending in the application.

II. Withdrawn rejections

The previously asserted rejection under 35 U.S.C. § 103 has been withdrawn in view of Applicant's arguments. Office Action at page 2.

III. Information Disclosure Statement

In regard to Exhibits A-F submitted with the response of July 6, 2009, "[t]he Examiner notes that applicants have not made *any* of the exhibits of record in an IDS." (Office Action at page 3, emphasis in original). There is no requirement, however, to submit references in the form of an IDS, and certainly not those submitted in *favor* of patentability.

> It should be noted that the rules are not intended to require information favorable to patentability such as, for example, evidence of commercial success of the invention. Similarly, the rules are not intended to require, for example, disclosure of information concerning the level of skill in the art for purposes of determining obviousness.

MPEP § 2001.4.

IV. Rejection under 35 U.S.C. 112, first paragraph

A. The rejection

Claims 14, 16-23, 25 and 26 are rejected as allegedly lacking in enablement. Office Action at pages 2-5. In previous Office Actions, the Examiner asserted that the prior art showed that IL-6 caused pancreatitis, and it was therefore obvious to treat pancreatitis with antagonists against IL-6 or IL-6R. Applicant argued that "the present claims are unobvious because the subject matter as a whole teaches away from the present invention. Even if the elements are found in the art, the art does not provide the requisite reason to combine them in

the manner claimed, with predictable results. And, even if a *prima facie* case could be made, it is rebutted by teaching away and unexpected results." Response of July 6, 2009, page 9. The Examiner found persuasive Applicant's arguments and withdrew the rejection under 35 U.S.C. § 103, and now asserts that the same arguments undermine enablement. In particular:

> Thus, while the Examiner has made a case *for* inhibition of IL-6 in acute pancreatitis (see 103 rejection in previous Office Actions), applicants have made a case *against* such.
>
> **Accordingly, there is no consensus in the art.**
>
> In this particular case, given the teachings in the art, there is no predictability about whether administration of IL-6 would be beneficial to patients having acute pancreatitis, nor how and when such should be administered; clearly, looking at the most recent reference cited by applicants in their most recent submission, timing would be critical.
>
> **There are *no* working examples in which *any* anti-IL-6 molecule was administered to any animal or human either having acute pancreatitis, or an accepted model of such.**
>
> The claims do not specify how or when the active agent is to be administered. Accordingly, the Examiner concludes that it is not predictable that the claimed invention would work at all. Nor is there sufficient disclosure to allow the skilled artisan to practice the claimed invention without substantial experimentation. All applicants have presented is the germ of an invention, and an invitation to determine how to practice that invention.
>
> . . . .
>
> The instant specification is not enabling because one cannot, following the guidance presented therein, practice the suggested method without first making a substantial inventive contribution.

Office Action at pages 4-5 (italics in original, bold text added). Applicant respectfully traverses the rejection.

B. The prior art is not determinative of enablement

The first flaw in the Examiner's argument is that enablement is determined by the specification *at the time of filing*, and may also be confirmed by post-filing evidence (*i.e.,* an essentially prospective inquiry), while obviousness is determined by the *prior art* (*i.e.,* an essentially retrospective inquiry). The teaching away found in the *prior art*, which undermines obviousness under 35 U.S.C. § 103, is not determinative of enablement of the *present specification* under 35 U.S.C. § 112, first paragraph. In other words, the prior art is not the same as the present specification.

It is axiomatic that a specification is *presumed* to be enabling unless the Examiner provides acceptable objective evidence or sound scientific reasoning showing that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. *See In re Marzocchi*, 169 USPQ 367 (C.C.P.A. 1971), *see also In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) ("Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling.").

Instead of providing objective evidence or sound scientific reasoning as applied to the *specification*, the enablement rejection relies on the prior art, and Applicant's characterization thereof. It would appear, indeed, that the rejection is made without consideration of Applicant's specification, which *does* set forth *working examples.* (See § IV(C), below). The Examiner fails to meet the burden of demonstrating that the specification is non-enabling, therefore.

C. The specification provides working examples

Contrary to the Examiner's assertion that "there are no working examples" are Examples 1 and 2 on pages 29-30 of the specification. Pancreatitis was induced in mice by injection of cerulein in Example 1, and cerulein plus LPS in Example 2. Pancreatitis was treated by antibodies against IL-6 receptor, leading to the conclusion that such antibodies "are effective, by suppressing the effects of IL-6, in treatment, amelioration of severity, and prevention of onset of acute pancreatitis." Example 1.

D. Cerulein-induced acute pancreatitis is an acceptable model

The Examiner asserts that Applicant has not demonstrated effectiveness in "an acceptable model" of acute pancreatitis. To the contrary, cerulein-induced pancreatitis is a very widely used model. A search on PubMed for "pancreatitis cerulein" identified 1248 documents, spanning from the 1973 to present day. *See* Exhibit G, listing documents 1-11 and 1231-1248 from a PubMed search.

Cerulein-induced acute pancreatitis is considered to be a relevant model of human pancreatitis and useful for the identification of therapy for human pancreatitis. For example, Exhibit H (Yamaguchi *et al. J. Pharmacol Exp. Ther.* 328: 256-262, 2009) describes how the human-approved drug risperidone was effective in treating cerulein-induced pancreatitis in a mouse model, leading to the conclusion that "Risperidone may provide a new therapy for the disease [pancreatitis]." *See* abstract.

Exhibit I (Michalski *et al. Gastroenterology* 132:1968-1978, 2007; Printed from NIH public access as pages 1-16) notes that previous research had demonstrated that "abdominal hyperalgia observed upon cerulein-induced murine pancreatitis was recently found to closely represent the pain syndrome seen in human disease" (Exhibit I, at page 2). The authors administered cannabinoids to mice 30 minutes before and 4 hours after administering cerulein, and found that, like pancreatitis in humans, cerulein-induced pancreatitis in mice shows an increase in cannabinoid receptors, and that cannabinoids are able to block pain. *Id.* They state that their latest findings "demonstrate the *in vivo* significance and therapeutic potential of cannabinoids in inflammation and pain associated with pancreatitis using human specimens and mouse models as test systems." *Id.*

Exhibit J (Alsfasser *et al. Arch. Surg.* 141: 670-676, 2006), examined the anti-inflammatory effects of recombinant human activated protein C in cerulein-induced pancreatitis in mice. Exhibit K (Gukovsky *et al. Am. J. Physiol Gastrointest Liver Physiol.* 294: G68-G79, 2008) examined a model of pancreatitis in mice in which alcohol and cerulein were found to reproduce human alcoholic pancreatitis, and thus shows how the basic cerulein-induced pancreatitis model can be adapted for different diseases.

In summary, the murine model of cerulein-induced pancreatitis has been described since at least the 1970s, remains widely used today, and is regarded as relevant to human disease and for the identification of treatments for human disease.

Under *In re Brana*, 51 F.3d 1560, 1567-68 (Fed. Cir. 1995), animal testing results are sufficient to establish whether one skilled in the art would believe that a pharmaceutical compound has an asserted clinical utility for the purposes of compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph. Given that numerous researchers in the art use the cerulein-induced pancreatitis mouse model to study treatment of human pancreatitis, the person of ordinary skill in the art would recognize that the examples described in the specification are sufficient to establish enablement of the present claims.

E. The claims are enabled

The present enablement rejection incorrectly relies on the prior art and overlooks the existence of working examples that demonstrate clinical utility by means of a well established and widely used model of human disease. Applicant respectfully requests reconsideration and withdrawal of the rejection.

V. Interview request

Applicant requests the courtesy of an interview if the Examiner persists in rejection of the claims. The Examiner is also invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed, Applicant hereby petitions under 37 C.F.R. §1.136 for such extensions and authorizes payment of any such extensions fees from the Deposit Account.

Respectfully submitted,

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